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Effect of intravenous adrenaline before arrival at the hospital in out-of-hospital cardiac arrest

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ABSTRACT

There is some evidence in prospective randomized clinical trials that the administration of adrenaline (AD) before admission for the treatment of out-of-hospital cardiac arrest did not improve survival to hospital discharge. The aim of this study was to evaluate our real-world experience regarding the efficacy of intravenous AD in out-of-hospital cardiac arrest at our university hospital. In this retrospective study, we enrolled and divided 644 patients into AD (AD administration before arrival at the hospital) and non-AD (no AD administration before arrival at the hospital) groups. The patient characteristics including age, sex, percentage of cardiac cause, location of cardiac arrest, and witnessed arrest were similar between the AD and non-AD groups. There were no significant differences between the AD and non-AD groups with regard to return of spontaneous circulation, survival to hospital admission, survival to hospital discharge, or good neurologic recovery at hospital discharge in all patients. In addition, we excluded the data of patients with extrinsic cause. We analyzed whether intravenous AD before arrival in patients with intrinsic cause was effective. The outcomes in the AD group were similar to those in the non-AD group. In conclusion, our study indicated that AD administration before arrival at the hospital for the treatment of out-of-hospital cardiac arrest did not improve the clinical outcome.

1. Introduction

Early access, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced care, including the use of intravenous drugs, should improve survival in sudden cardiac arrest. The administration of adrenaline (AD) has been advocated during CPR in cardiac arrest for decades [1]. The 2005 guidelines of both the American Heart Association and the European Resuscitation Council recommend its use [2,3]. AD was shown to be an independent predictor of a poor outcome in a large retrospective registry study [4]. AD has been shown to have beneficial short-term effects in animal studies [5,6]. On the other hand, there has been some concern regarding the potential harmful effects of AD on post cardiac arrest myocardial function and cerebral function, and there is little evidence from clinical trials that the use of AD for the treatment of cardiac arrest improves survival [7,8]. The survival outcomes in human studies have been controversial [9–11].

Several prospective randomized clinical trials have recently indicated that the use of AD before admission for the treatment of out-of-hospital cardiac arrest (OHCA) did not improve survival to hospital discharge [12,13]. In a prospective, randomized controlled trial, patients with intravenous access and drug administration had higher rates of short-term survival with no statistically significant improvements in survival to hospital discharge or long-term survival compared to patients who received advanced cardiac life support (ACLS) without intravenous drug administration following OHCA [12]. In addition, Jacobs et al. reported that patients who received AD during cardiac arrest had no statistically significant improvement in survival to hospital discharge, although there was a significantly improved likelihood of achieving return of spontaneous circulation (ROSC) in a double-blind randomized placebo-controlled trial [13].

Therefore, in this study, we aimed to evaluate our real-world experience regarding the efficacy of intravenous AD before arrival at the hospital in OHCA from the Fukuoka University Registry (FU-Registry).

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2. Methods

2.1. Study patients and design

Six hundred forty-four patients who experienced cardiac arrest between April 2006 and March 2011 at the Department of Emergency and Critical Care Medicine, Fukuoka University Hospital, Fukuoka, Japan were enrolled. The enrollment was performed using our database of FU-Registry. Our protocol was approved by the hospital ethics committee. Patients received either ACLS with intravenous AD before arrival at the hospital (AD group) or ACLS without intravenous AD before arrival at the hospital (non-AD group). Intravenous AD was given after the initiation of CPR and initial defibrillation (if appropriate) following successful placement of an intravenous line consistent with ACLS standards according to the modified 2005 American Heart Association guidelines [3]. The paramedics were able to provide ACLS and defibrillation with automated external defibrillators.

The patient characteristics (age, sex, and medical history), cardiac arrest circumstances (arrest location, witnessed, bystander CPR, defibrillation, AD given), electrocardiographic (ECG) rhythms, emergency medical services (EMS) response times, and outcomes were recorded by EMS personnel and subsequently by physicians. The ambulance crew recorded the time of arrival at the patient's side, the time when CPR was started, the time of defibrillation, the time when transport to the hospital was started, and the time of arrival at the hospital. The immediate outcome was reported as dead on arrival, dead in emergency room, or admitted to hospital alive.

The initial cardiac arrest rhythm was defined as ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA), or asystole. Shockable rhythm was defined as VF and pulseless VT. PEA and asystole are non-shockable rhythms. The initial rhythm was based on information obtained from the first ECG recording after arrival of the ambulance crew and on whether or not the patient was defibrillated.

2.2. Study outcomes

The primary endpoint was survival to hospital discharge with secondary endpoints of ROSC, survival to hospital admission, and good neurologic recovery at hospital discharge. Cerebral Performance Category (CPC) at hospital discharge was used as a neurological outcome. CPC scores are defined as: 1 – normal function; 2 – mild to moderate disability; 3 – severe disability; 4 – vegetative state; and 5 – dead. The patients with survival to hospital discharge were divided into two groups: fully awake and other. Good neurologic recovery was defined as CPC 1 or 2.

2.3. Statistical analysis

Differences in patient and study characteristics were assessed using Pearson's chi-square test and the *t*-test for categorical and continuous data, respectively. Odds ratios (OR) and 95% confidence intervals were derived for primary and secondary outcomes. Logistic regression was used to adjust for potential confounders on the effect of treatment with AD on primary and secondary outcomes. Analysis was performed on an intention-to-treat basis and per-protocol basis using StatView 5.0 statistical software. All statistical tests were two-sided with a significance level of 0.05.

3. Results

3.1. Patient characteristics

Six-hundred forty-four patients who experienced OHCA were enrolled (Fig. 1). Of those, 131 patients were not eligible due to insufficient medical records, cardiac arrest in our hospital, and transfer from another hospital. We also excluded 21 patients with age younger than 18 years. Therefore, this study included 492 adult patients: 49 with AD administration and 443 without AD administration. Table 1 shows the characteristics of all patients in the AD and non-AD groups. Characteristics such as age, gender, percentage (%) of cardiac cause, location of cardiac arrest, initial rhythm, and defibrillation before arrival at the hospital were similar in both groups. The incidence of witnessed cardiac arrest by bystander in the AD group was significantly higher than that in the non-AD group. In patients with intrinsic cause, there were no significant differences in those characteristics between the groups (data not shown). The cause of arrest in all cases is shown in Table 2. There were 333 with intrinsic causes and 159 with extrinsic causes. There were no differences in the cause between the AD and non-AD groups.

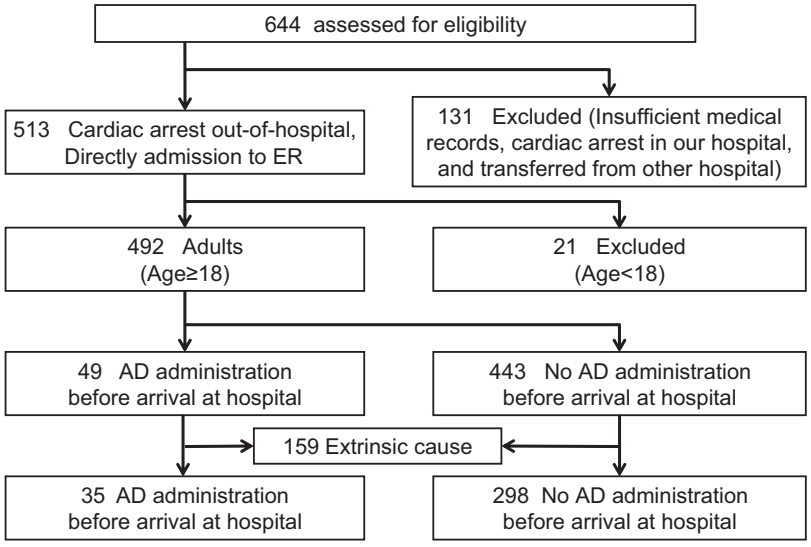

Fig. 1. Study profile. ER, emergency room; AD, adrenaline.

Table 1
Patient characteristics.

	All (n = 492)	Non-AD group (n = 443)	AD group (n = 49)	P value Non-AD versus AD
Age (years)	64 ± 18	64 ± 18	63 ± 18	0.882
Male, n (%)	324 (66)	291 (66)	33 (67)	0.816
Indoor location of cardiac arrest, n (%)	379 (77)	342 (77)	37 (76)	0.79
Cardiac arrest before ambulance arrival, n (%)	443 (90)	398 (90)	45 (91)	0.658
Bystander CPR, n (%)	261 (53)	236 (53)	25 (51)	0.764
Witnessed cardiac arrest, n (%)				
By bystander	167 (34)	141 (32)	26 (53)	0.003
By ambulance crew	47 (10)	43 (10)	4 (8)	0.727
Initial cardiac arrest rhythm, n (%)				
Pulseless electrical activity	139 (28)	124 (28)	15 (30)	0.706
Ventricular fibrillation/tachycardia	75 (15)	63 (14)	12 (25)	0.059
Asystole	277 (56)	255 (58)	22(45)	0.087
Defibrillation before arrival at the hospital, n (%)	84 (17)	71 (16)	13 (27)	0.071
Intravenous access before arrival at the hospital, n (%)	143 (29)	94 (21)	49 (100)	<0.001
Onset – call (min)	4.3 ± 6.7	4.5 ± 7.1	3.7 ± 4.1	0.527
Call – arrival at patient's side (min)	7.7 ± 4.2	7.6 ± 4.0	8.4 ± 5.5	0.169
Arrival at patient's side – arrival at the hospital (min)	18.3 ± 6.3	18.4 ± 6.3	18.1 ± 6.1	0.805
Arrival at patient's side – adrenaline i.v. (min)	23.6 ± 8.0	25.1 ± 7.1	12.3 ± 5.4	<0.001
Cardiac arrest on arrival at the hospital, n (%)	437 (89)	397 (90)	40 (82)	0.092
Cardiac arrest rhythm on arrival at the hospital, n (%)				
Pulseless electrical activity	104 (24)	94 (24)	10 (24)	0.919
Ventricular fibrillation/tachycardia	29 (7)	24 (6)	5 (12)	0.132
Asystole	303 (69)	278 (70)	25 (61)	0.232

3.2. Outcomes for patients in the AD and non-AD groups

Table 3 shows the results of the analysis for primary and secondary outcomes stratified according to AD administration. In all patients, the incidences of ROSC, survival to hospital admission, survival to discharge, and good neurologic recovery in the AD group were similar to those in the non-AD group (Table 3a). In a comparison of the AD group to the non-AD group, the OR was 0.88 for ROSC (p = 0.808) for survival to hospital admission, 1.16 (p = 0.724) for survival to discharge, and 0.52 (p = 0.445) for good neurologic recovery at hospital discharge. In addition, we also excluded the data of patients with extrinsic cause and analyzed whether intravenous AD before arrival in patients with intrinsic cause was effective in Table 3b. The outcomes in the AD group were similar to those in the non-AD group.

We also evaluated the efficacy of AD in patients with shockable OHCA in Table 4. In patients with shockable OHCA (all cause or intrinsic cause cases), the incidences of ROSC, survival to hospital admission, survival to discharge, and good neurologic recovery in the AD group were similar to those in the non-AD group. Thus, there were no significant differences between the AD and non-AD groups in terms of the clinical outcomes.

Table 2
Cause of cardiac arrest.

	All (n = 492)	Non-AD group (n = 443)	AD group (n = 49)
Intrinsic cause, n (%)	333 (68)	298 (67)	35 (71)
Cardiologic disease	169 (34)	147 (33)	22 (45)
Respiratory disease	23 (5)	19 (4)	4 (8)
Neurological disease	22 (5)	20 (5)	2 (4)
Digestive disease	9 (2)	9 (2)	0 (0)
Others (unknown)	110 (22)	103 (23)	7 (14)
Extrinsic cause, n (%)	159 (32)	145 (33)	14 (29)
Trauma	53 (11)	50 (11)	3 (6)
Neck hanging	54 (11)	51 (12)	3 (6)
Airway trouble	28 (6)	22 (5)	6 (12)
Drowning	16 (3)	14 (3)	2 (4)
Others	8 (2)	8 (2)	0 (0)

4. Discussion

AD has been a standard of ACLS care since its inception. In the present study that considered real-world experience, the administration of AD before arrival at the hospital for the treatment of OHCA did not improve ROSC, survival to hospital admission, survival to hospital discharge, or good neurologic recovery at hospital discharge.

AD is thought to aid resuscitation mainly by its α-adrenergic effects. The survival outcomes in human studies have been controversial [9–11]. However, the potential adverse effects of AD include decreased total forward cardiac output, increased myocardial oxygen consumption, myocardial dysfunction post-resuscitation, and increased intrapulmonary shunting [14,15]. We did not confirm a previous observational finding that intravenous AD was an independent predictor for a poor outcome [4]. Our results are consistent with those of a multicenter study by Stiell et al., who found no difference in survival after implementing intravenous drug administration during OHCA [16], and two recent prospective randomized clinical trials [12,13]. This study showed that AD administration before admission had no significant effect on short-term survival, and there is no reason to expect any difference in long-term survival or neurologic recovery.

Patients with intravenous access and drug administration had higher rates of short-term survival (more frequently ROSC) [12]. ROSC is an increasingly important clinical endpoint regarding the influence of post-resuscitation care interventions on survival to hospital discharge [17,18]. Jacobs et al. clearly demonstrated that AD was superior to placebo for achieving ROSC [13]. A clinical study that evaluated high-dose AD showed that it improved short-term results without improving long-term outcomes [19]. In our study, we found no difference in short-term effects (ROSC and survival to hospital admission). The negative post-resuscitation effects of AD have also been reported to be more prominent after longer, more clinically relevant periods of cardiac arrest (e.g. 4–6 min) than after short periods of cardiac arrest (e.g. 2 min) [20]. This difference may have influenced our results, but we do not have sufficient data regarding the duration of cardiac arrest. Moreover, we did not know the dose of AD in this study, and randomized trials of AD

Table 3
Outcomes for patients in the AD and non-AD groups in all patients (a) and patients with intrinsic cause (b).

a. All patients

Outcomes	Non-AD group (n = 443), n (%)	AD group (n = 49), n (%)	OR (95% CI)	P value
Return of spontaneous circulation (ROSC)	204 (46)	21 (43)	0.88 (0.48–1.59)	0.671
Survival to hospital admission	155 (35)	18 (37)	1.08 (0.56–1.99)	0.808
Survival to hospital discharge	64 (14)	8 (16)	1.16 (0.52–2.58)	0.724
Good neurologic recovery at hospital discharge (CPC 1–2)	28 (44)	2 (25)	0.43 (0.08–2.29)	0.321

b. Patients with intrinsic cause

Outcomes	Non-AD group (n = 298), n (%)	AD group (n = 35), n (%)	OR (95% CI)	P value
Return of spontaneous circulation (ROSC)	144 (48)	15 (43)	0.80 (0.40–1.63)	0.541
Survival to hospital admission	104 (35)	13 (37)	1.10 (0.53–2.28)	0.793
Survival to hospital discharge	40 (13)	6 (17)	1.33 (0.52–3.42)	0.547
Good neurologic recovery at hospital discharge (CPC 1–2)	22 (55)	2 (33)	0.41 (0.07–2.50)	0.333

AD, adrenaline; OR, odds ratio; CI, confidence interval; CPC, Cerebral Performance Category. Data of good neurologic recovery are shown in the patients with survival to hospital discharge.

in cardiac arrest have compared high-dose versus standard-dose AD, without reference to placebo or the non-administration of AD [21–23]. All of these trials demonstrated that high-dose AD was superior for achieving ROSC, however, they failed to demonstrate better survival to hospital discharge.

Since AD administration was not associated with the clinical outcome, we also analyzed contributors to patient outcome in all patients (Supplementary Figure). Logistic regression modeling was performed to control for the effect of potential confounders on the relationship between AD administration and patient outcome. Independent predictors for ROSC were witnessed arrest and cardiac cause and defibrillation before arrival at the hospital, those for survival to hospital admission were witnessed arrest, cardiac cause, and initial shockable rhythm, that for survival to discharge was witnessed arrest. Thus, in this study, witnessed arrest was a common and strong predictor for ROSC, survival to hospital admission, and survival to discharge. In addition, in patients with intrinsic cause, witnessed arrest was a common and strong predictor for ROSC and survival to hospital admission (data not shown). Witnessed arrest, but not AD administration before arrival at the hospital, may strongly affect the clinical outcome. To support this observation, some trials have demonstrated that AD is superior for achieving ROSC, however they failed to demonstrate better survival to hospital discharge [22,23].

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2012.07.001.

Several studies have identified dissimilar etiologies in subgroups with shockable and nonshockable rhythms [24], and it seems reasonable that there are differences in treatment strategies [25]. Fifteen percent of our patients had a shockable rhythm. Well-controlled prospective randomized clinical trials have shown higher percentages of patients with a shockable rhythm (33% [12] and 45% [13]). Thus, the factor of an initial shockable rhythm was included in logistic regression modeling. An initial shockable rhythm was an independent predictor for survival to hospital admission, but not for survival to discharge. However, our study was not powered for this analysis and no conclusions should be drawn.

In this study, there were several specific patient characteristics and clinical outcomes compared to those as previously reported. As noted before, the incidence of shockable rhythm was relatively low in this study. In addition, the incidence of survival to hospital discharge (15%) was relatively high compared to previous reports (10% [12] and 3% [13]), and the incidence of cardiac cause (34%) was

Table 4
Outcomes for patients in the AD and non-AD groups in patients with shockable OHCA.

a. All patients

Outcomes	Non-AD group (n = 63), n (%)	AD group (n = 12), n (%)	OR (95% CI)	P value
Return of spontaneous circulation (ROSC)	47 (75)	7 (58)	0.48 (0.13–1.72)	0.257
Survival to hospital admission	44 (70)	7 (58)	0.61 (0.17–2.15)	0.436
Survival to hospital discharge	29 (46)	3 (25)	0.39 (0.10–1.58)	0.188
Good neurologic recovery at hospital discharge (CPC 1-2)	19 (66)	2 (67)	1.05 (0.09–13.08)	0.968

b. Intrinsic cause

Outcomes	Non-AD group (n = 58), n (%)	AD group (n = 11), n (%)	OR (95% CI)	P value
Return of spontaneous circulation (ROSC)	44 (76)	6 (55)	0.38 (0.10–1.45)	0.156
Survival to hospital admission	41 (71)	6 (55)	0.50 (0.13–1.85)	0.298
Survival to hospital discharge	27 (47)	3 (27)	0.43 (0.10–1.79)	0.246
Good neurologic recovery at hospital discharge (CPC 1–2)	18 (67)	2 (67)	1.00 (0.08–12.56)	>0.999

AD, adrenaline; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; CI, confidence interval; CPC, Cerebral Performance Category. Data of good neurologic recovery are shown in the patients with survival to hospital discharge.

relatively low (70% [12] and 90% [13]). These differences may also affect the efficacy of AD administration.

4.1. Study limitations

This study has several limitations. First, it was a retrospective clinical study and not a placebo-controlled, randomized study. Second, we were unable to assess the influence of CPR quality or the timing of AD administration during resuscitation on our findings. AD administration varied depending on the successful establishment of intravenous access and variations in resuscitation procedures. In addition, we did not exclude the possibility that other drug regimens might improve the outcome. Third, sudden cardiac arrests were induced by intrinsic and extrinsic causes. Intrinsic cause mainly contained cardiologic diseases, such as acute myocardial infarction [26] and ventricular fibrillation including Brugada syndrome [27]. Since we did not have enough information about them, it might affect the efficacy of intravenous AD. Fourth, only 10% of the patients in this study received AD from paramedics, which is much less than in previous reports. This contributes to why the study was underpowered for the endpoint. Finally, this is a single-center study and the results may not be generalized to systems with different training, infrastructure, treatment protocols, or quality of CPR.

5. Conclusions

Our study indicated that the use of AD administration before arrival at the hospital for the treatment of OHCA did not improve clinical outcomes in real-world experience at our university hospital. The findings of this study are clinically important in that they did not support the continued use of AD in cardiac arrest as currently recommended.

Conflicts of interest

No conflicts of interest to declare.

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